REMARKS

Claim 1 has been amended to provide antecedent basis for the term "affinity" in line 10 and to clarify the relationship between the demitopes as requested by the Office. Further, the claim is clarified by making explicit its inherent limitation that the interaction between the first and second substance under the conditions of the assay is not known, so that it is the interaction between the first and second substance that is to be tested. Support for this amendment is found, for example, on page 2, beginning at the last line (in paragraph [0007]), in paragraph [0008], and throughout the specification.

Claim 1 has further been amended to make specific what has already been recognized by the Office – that the substances to be tested are heterologous to the demitopes whose assembly will result in the requisite paratope or binding site.

Claim 5 has been clarified by spelling out nuclear magnetic resonance (NMR) and clarifying that the NMR spectrum of the reporter is determined.

Claim 9 has been clarified by changing "small molecule" to "non-peptide ligand" which may be more readily interpreted.

No new matter has been added and entry of the amendment is respectfully requested.

Formal Matters

As examination has been performed only with respect to claims 1-11, non-elected claims 12-22 have been canceled without prejudice to their pursuance in a divisional application.

As noted above, antecedent basis has been provided for "the affinity" in claim 1 and the word "complementary" has been added to clarify that the demitopes are indeed able to form the

paratope. It is believed this limitation was already inherent since the claim requires that the demitopes when assembled form a paratope that binds the reporter. Thus, by definition, the demitopes must be complementary.

Further, claim 5 has been amended to provide the spelled-out meaning of the familiar acronym NMR. Claim 9 has been amended to delete the term "small molecule."

It is believed the foregoing amendments are responsive to all rejections under 35 U.S.C. § 112, paragraph 2, with the exception of that applied to claim 6 which is discussed as follows:

Claim 6 is said to be unclear because the effect of a toxin would take some time to observe, and therefore is interpreted as not "immediate." However, in the context of the present invention, "immediate" is not used to designate an instantaneous result. Rather, "immediate" is defined on page 4, in paragraph 17, as requiring only two things – *i.e.*, that there is no cascade of reactions needed to obtain a detectable signal but that the signal flows directly from the binding of the reporter to the paratope. This distinguishes, for example, the yeast 2-hybrid system where successful binding of two substances generates a polymerase which must in turn act on an expression system which must in turn produce an RNA which must in turn produce a protein which must in turn produce a signal. Second, the response is required to be linear – *i.e.*, it is stronger, the stronger the binding of the binding of the two substances to be tested. Both of these are true of the binding of a toxin as the toxin directly kills the surrounding cells in proportion to its concentration which is inversely proportional to the affinity of binding of the two substances to form the assembled paratope.

In light of the definition of "immediate" in the specification, it is believed that claim 6 is clear.

The Rejections Over the Art

It is noted with appreciation that claim 6 is not rejected over the art. As claim 6 has been clarified, this claim should be in a position for immediate allowance.

Claims 1-4 and 9-11 were rejected over the combination of two documents – Arndt, *et al., J. Mol. Biol.* (2001) 312:221-228 in view of Kranz, *et al., Proc. Natl. Acad. Sci. USA* (1981) 78:5807-5811. It is noted that claim 9 is included in this objection only because the nature of a "small molecule" appeared unclear. In view of the amendment to claim 9, it is clear that this claim is free of the rejection as the interactions described both by Kranz and by Arndt, is that between two proteins, not a protein and a non-peptide ligand.

Respectfully, it is believed that there is no motivation to combine Arndt with Kranz and further that even when combined, these documents do not suggest the invention as now claimed.

Kranz is directly related to claim 4 which mandates that the detectable signal be fluorescence-quenching or fluorescence-enhancement. The fact that the fluorescence signal changes when bound to another material, such as an antibody, is, of course, acknowledged prior art. Kranz is discussed in the application itself in paragraph 25 on page 6. As indicated in the specification, this known phenomenon is for the first time seen to be applicable to the method of the invention. As noted by the Office, the method of Kranz is used to detect mixing and matching of the demitopes themselves, not in a method to determine interaction of substances heterologous to the demitopes. Although this was not explicitly in the claims as filed, the Office correctly assumed that this was the intent.

As further noted by the Office, the Arndt document discloses an alternative method to associate demitopes which results in an antibody fragment that is presumably more stable than that

provided by the associations inherent in F_v and F_{ab} fragments. It is further designed to avoid the dimerization which appears to occur with F_{scv} moieties. Arndt is acknowledged as failing to suggest the use of a reporter to provide an immediate signal for the assembly of the paratope; rather, Arndt merely determines whether the paratope can bind its known antigen using conventional techniques. The only motivation suggested by the Office to combine Arndt and Kranz is that the use of a reporter (Kranz) would reduce the number of steps required to diagnose the appropriate assembly (Arndt).

First, however, any combination to result in the invention would require further modification of the Arndt document. Antibodies to a fluorescent moiety would have to have been studied by Arndt – on the contrary, the antibodies studied are directed to phosphoryl choline. More importantly, in the work of Arndt, the interaction of the counterparts to the first and second substances of the invention was specifically designed to occur under the conditions employed; the known interaction of these substances was used as a vehicle to assemble an antibody. Arndt does not teach, as required by the invention, the assembly of an antibody as a vehicle to determine the interaction between two substances under conditions where their interaction and affinity is not known in the first place. Thus, as is clear from the claims, the binding of the first substance to the second substance, or the affinity of any binding, is to be tested. It may be understood that the two substances bind under some conditions, but not clear whether they bind under conditions of the assay.

For these two reasons, simple combination of Kranz with Arndt does not yield the invention – Arndt does not use an antibody to a fluorescent substance and Arndt does not determine the interaction of substances whose interaction under the assay conditions is not predictable.

Not only does the combination of these documents not result in the invention, there is no acceptable motivation to combine them. The motivation cited by the Office arises after the fact: to the extent the combination can be construed to suggest the invention, it is only the invention itself that has seen fit to combine them. Neither document on its face suggests combination with the other and the nature of the problem to be solved is different in each case. The problem to be solved in Kranz is to test the ability of homologous *vs.* heterologous H and L chains to associate in preparations of hapten-specific monoclonal antibodies. The purpose of the Arndt study is to provide an improved form of antibody fragment that will still retain its antibody characteristics by using the known assembly technique of the heterodimeric coiled coil named WinZip-A2B1. Neither document is particularly well known to those in the art. Thus, none of the three acceptable criteria for motivation as outlined in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) is satisfied by these documents. The holding in *Rouffet* recognizes only these three factors as acceptable rationale for support of motivation to combine. A copy of this decision is attached.

Thus, in light of the lack of motivation to combine these documents and the failure of these documents to suggest the invention when they are combined makes proper the withdrawal of the rejection of claims 1-4 and 9-11.

The rejections of claims 5, 7 and 8 fail for similar reasons. First, it is unclear why Kranz is included in the rejection of claim 5 since there is no fluorescent signal required. It is assumed that the rejection is in fact over Arndt, *et al.,* in view of Koide (U.S. 6,673,901).

Like Kranz, Koide teaches only acknowledged prior art – that the NMR signal of a compound will differ depending on its association with other materials. Column 28 of Koide is cited as indicating that NMR has been used to determine such associations. It appears from a

reading of columns 28, 29 and 30, that the NMR being taken is that of the antibody itself as shown in Figure 14 rather than that of the reporter as now made explicit in claim 5. Furthermore, the combination of Koide with Arndt fails to suggest the invention since there is no suggestion in either document that NMR spectra of bound substances be used to detect the formation of a paratope. The use of NMR in Koide is simply to explore the contours of an already established paratope. Neither document seeks to use the formation of a paratope to indicate the interaction of two substances whose interaction under the conditions of the assay is not predictable.

As was the case with regard to the combination of Arndt with Kranz, there is no suggestion in either document to make the combination. The problems to be solved are different (the problem to be solved in Koide is to provide unique fibronectin type m antibodies and that in Arndt, as described above, is to provide an improved form of effective antibody fragment). Neither document has a high profile in the art. Thus, none of the *Rouffet* motivating factors is present, and as previously, the combination, once made, does not result in the invention.

As to claims 7 and 8, in which the combination of Arndt and Kranz is further combined with Griffin, *et al., Science* (1998) 281:269-271 (claim 7) and with Empedocles, *et al.* (U.S. 2001/0055764), similar comments apply. Applicants are well aware that fluorescence from inside of live cells can be observed as well as being conversant with wide field microscopy as an observation tool. Because the combination of Arndt and Kranz fails to suggest even the broader aspects of the invention, the notation by Griffin that fluorescence from within a cell can be observed seems to add little. Clearly there is no motivation to combine Griffin with either of the foregoing documents since Griffin is concerned with introducing a fluorescent molecule label to identify a specific protein which has intentionally been provided with a binding site. This enterprise has

nothing whatsoever to do with the present invention, although it does indicate that the method of the invention is appropriate for measuring intracellular events. Similarly, the purposes for which Empedocles employs wide field microscopy has nothing to do with the pending claims – incorporating semiconductor nanocrystal conjugates has no particular relevance to the present invention. Why detecting semiconductor nanocrystals by wide field microscopy would be in any way related to detecting fluorescence changes when a fluorescent substance is bound to a paratope eludes applicants. Claim 8, to which this document is applied, has no requirement for semiconductor nanocrystal conjugates at all.

CONCLUSION

The claims have been amended to respond to the rejections under 35 U.S.C. § 112, paragraph 2. The definition of "immediate" in paragraph 17 of the application has been called to the attention of the Office in response to the rejection of claim 6.

Claim 6, and it appears that claim 9 as amended, were not rejected over the art. As to the rejections of the remaining claims, it has been shown that even if combined, Arndt and the additional cited documents do not suggest the invention as claimed nor is there any motivation to make these combinations. Thus, applicants believe that claims 1-11 as amended are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512010500.

Respectfully submitted,

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